The change to amended claim 21 is merely to correct a typographical error and does not involve new matter.

The changes to the claims do not involve new matter and applicants respectfully request entry of them.

In view of the preceding amendments and the remarks which follow, applicants respectfully request that the Patent Office enter the amendments to the claims.

Moreover, in view of the changes hereinabove and the following comments, applicants respectfully request that the Patent Office reconsider and withdraw the various grounds for objection and rejection set forth in the July 12, 1993 Office Action.

OBJECTION TO THE SPECIFICATION UNDER 35 U.S.C. §112

At paragraph 20 of the Office Action, the Patent Office objected to the specification under 35 U.S.C. § 112, first paragraph, for reasons of record.

Applicants respectfully traverse the Examiner's basis for objecting to the specification for the reasons which follow.

THE REJECTION IS BASED ON FACTUALLY FALSE ASSUMPTIONS

The basis for the rejection is twofold.

First, applicants allegedly have not provided a sufficient written description of the invention with respect to the *in vivo* operability of the protein to enable one of ordinary skill in the art to use applicant's invention for use in humans.

Second, applicants allegedly are required to submit evidence

of *in vivo* tests in order to show *in vivo* operability of the protein to enable one skilled in the art to use the claimed invention in humans.

THE LEGAL STANDARD FOR MEETING THE DESCRIPTION REQUIREMENT

The test is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter. *In re Kaslow,* 707 F.2d 1366, 217 USPQ 1089 (Fed. Cir. 1983).

The claimed invention includes method for regulating functional CD28 positive T cell responses, method for preventing the binding of the CD28 receptor to the B7 antigen so as to inhibit functional T cell responses, method for treating a subject with a disease associated with the interaction of B7 with CD28 positive T cells, method for inhibiting CD28 positive T cell proliferation in graft versus host disease, method for regulating the level of a cytokine *in vivo*.

THE LEGAL STANDARD FOR ENABLEMENT

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *United States v. Telectronics,* Inc., 856 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988).

No authority has been cited and we have been able to find none which requires that in order to secure a patent for a pharmacologically active substance and uses thereof, applicants must provide *in vivo* testing.

In fact, the courts have maintained that *in vivo* testing is

not a requirement. *In re Isaacs and Lindenmann,* 877 F.2d 1582, 146 USPQ 193, 195 (CCPA 1965).

In *Isaacs* the court held that the mere fact that the claimed invention may have possible utility *in vivo* does not warrant disregard of *in vitro* activity where the claims are not limited to an *in vivo* use (*In re Isaacs and Lindenmann*).

In view of the court's holding that an unchallenged allegation of *in vitro* utility is sufficient for purposes of 35 U.S.C. §101, rejections under 35 U.S.C. §112, first paragraph, concerning whether or not the specification states what quantities safely may be administered to a subject human or animal, how the material may be administered, or what the effect of any quantity of this material has on a living subject becomes moot (*In re Isaacs and Lindenmann* at page 197, left column, last paragraph).

BOTH LEGAL STANDARDS HAVE BEEN MET

APPLICANTS HAVE ADEQUATELY DESCRIBED THE CLAIMED INVENTION

Applicants respectfully disagree with the Examiner's statements that there is an insufficient written description of the invention, i.e., the claimed B7Ig and CD28Ig fusion proteins, and the manner of using it.

Applicants have taught the following:

> "Alternatively, the ligand for CD28, its fragments or derivatives, may be introduced in a suitable pharmaceutical carrier in vivo, i.e. administered into a human subject for treatment of pathological conditions such as immune system diseases or cancer. Introduction of the ligand in vivo is expected to result in interference with T cell/B cell interactions as a result of binding of the ligand to T cells. The prevention of normal T cell/B cell contact may result in decreased T cell activity, for example, decreased T cell proliferation.

In addition, administration of the B7 antigen in vivo is expected to result in regulation of in vivo levels of cytokines, including, but not limited to, interleukins, e.g. interleukin ("IL")-2, IL-3, IL-4, IL-6, IL-8, growth factors including tumor growth factor ("TGF"), colony stimulating factor ("CSF"), interferons ("IFNs"), and tumor necrosis factor ("TNF") to promote desired effects in a subject. It is anticipated that ligands for CD28 such as B7Ig fusion proteins and Fab fragments may thus be used in place of cytokines such as IL-2 for the treatment of cancers in vivo. For example, when the ligand for CD28 is introduced in vivo it is available to react with CD28 antigen positive T cells to mimic B cell contact resulting in increased production of cytokines which in turn will interact with B cells.

Under some circumstances, as noted above, the effect of administration of the B7 antigen, its fragments or derivatives in vivo is stimulatory as a result of aggregation of the CD28 receptor. The T cells are stimulated resulting in an increase in the level of T cell cytokines, mimicking the effects of T cell/B cell contact on triggering of the CD28 antigen on T cells. In other circumstances, inhibitory effects may result from blocking by the B7 antigen of the CD28 triggering resulting from T cell/B cell contact. For example, the B7 antigen may block T cell proliferation. Introduction of the B7 antigen in vivo will thus produce effects on both T and B cell mediated immune responses. The ligand may also be administered to a subject in combination with the introduction of cytokines or other therapeutic reagents. Alternatively, for cancers associated with the expression of B7 antigen, such as B7 lymphomas, carcinomas, and T cell leukemias, ligands reactive with the B7 antigen, such as anti-B7Ig monoclonal antibodies, may be used to inhibit the function of malignant B cells.

Because CD28 is involved in regulation of the production of several cytokines, including TNF and gamma interferon (Lindsten et al., supra, (1989)), the ligand for CD28 of the invention may be useful for in vivo regulation of cytokine levels in response to the presence of infectious agents. For example, the ligand for CD28 may be used to increase antibacterial and antiviral resistance by stimulating tumor necrosis factor (TNF) and IFN production. TNF production seems to play a role in antibacterial resistance at early stages of infection (Havell, J. Immunol. 143:2894-2899 (1990)). In addition, because herpes virus infected cells are more susceptible to TNF-mediated lysis than uninfected cells (Koff and Fann, Lymphokine Res. 5:215 (1986)), TNF may play a role in antiviral immunity" (specification at page 24, lines 14-35 through page 26, lines 1-3).

"In addition, B7Ig fusion proteins as described above may be used to regulate T cell proliferation. For example, the soluble CD28Ig and B7Ig fusion proteins may be used to block T cell proliferation in graft versus host (GVH) disease which accompanies allogeneic bone marrow transplantation. The CD28-mediated T cell proliferation pathway is cyclosporine-resistant, in contrast to proliferation driven by the CD3/Ti cell receptor complex (June et al., 1987, supra). Cyclosporine is relatively ineffective as a treatment for GVH disease (Storb, Blood 68:119-125 (1986)). GVH disease is thought to be mediated by T lymphocytes which express CD28 antigen (Storb and Thomas, Immunol. Rev. 88:215-238 (1985)). Thus, the B7 antigen in the form of B7Ig fusion protein, or in combination with immunosuppressants such as cyclosporine, for blocking T cell proliferation in GVH disease. In addition, B7Ig fusion protein may be used to crosslink the CD28 receptor, for example by contacting T cells with immobilized B7Ig fusion protein, to assist in recovery of immune function after bone marrow transplantation by stimulating T cell proliferation.

The fusion proteins of the invention may be useful to regulate granulocyte macrophage colony stimulating factor (GM-CSF) levels for treatment of cancers (Brandt et al., N. Eng. J. Med. 318:869-876 (1988)), AIDS (Groopman et al., N. Eng. J. Med. 317:593-626 (1987)) and myelodysplasia (Vadan-Raj et al., N. Eng. J. Med. 317:1545-1551 (1987)).

Regulation of T cell interactions by the methods of the invention may thus be used to treat pathological conditions such as autoimmunity, transplantation, infectious diseases and neoplasia.

In a preferred embodiment, the role of CD28-mediated adhesion in T cell and B cell function was investigated using procedures used to demonstrate intercellular adhesion mediated by MHC class I (Norment et al., (1988) supra) and class II (Doyle and Strominger, (1987) supra) molecules with the CD8 and CD4 accessory molecules, respectively. The CD28 antigen was expressed to high levels in Chinese hamster ovary (CHO) cells and the transfected cells were used to develop a CD28-mediated cell adhesion assay, described infra. With this assay, an interaction between the CD28 antigen and its ligand expressed on activated B lymphocytes, the B7 antigen, was demonstrated. The CD28 antigen, expressed in CHO cells, was shown to mediate specific intracellular adhesion with human lymphoblastoid and leukemic B cell lines, and with activated murine B cells. CD28-mediated adhesion was not dependent upon divalent cations. A mAb, BB-1, reactive with B7 antigen was shown to inhibit CD28-mediated adhesion. Transfected COS cells expressing the B7

> antigen were also shown to adhere to $CD28^+$ CHO cells; this adhesion was blocked by mAbs to CD28 receptor and B7 antigen. The specific recognition by CD28 receptor of B7 antigen, indicated that B7 antigen is the ligand for the CD28 antigen.
>
> The results presented herein also demonstrate that antibodies reactive with CD28 and B7 antigen specifically block helper T_h-mediated immunoglobulin production by allogeneic B cells, providing evidence of the role of CD28/B7 interactions in the collaboration between T and B cells." (specification at page 26, lines 5-35 through page 28, lines 1-18).

Applicants respectfully contend that the claimed fusion proteins and methods of using it have been adequately described in accordance with 35 U.S.C. §112, first paragraph. It would be clear to one skilled in the art that the claimed invention may be in a variety of dosage forms which include, but are not limited to, liquid solutions or suspensions, tablets, pills, powders, suppositories, polymeric microcapsules or microvesicles, liposomes, and injectable or infusible solutions. The preferred form depends upon the mode of administration and the type of application.

For example, for diagnostic use the claimed invention may be used to activate T cells *in vitro* and the T cells so activated may be used *in vivo* in adoptive therapy (specification at page 24, first paragraph).

The most effective mode of administration and dosage regimen for the claimed invention will depend upon the severity and course of the disease, the subject's health and response to treatment and the judgment of the treating physician. Accordingly, the dosages of the claimed invention should be titrated to the individual subject.

APPLICANTS HAVE ENABLED THE CLAIMED INVENTION

Applicants have met the test of enablement.

In this regard, applicants have taught the *in vitro* application of the claimed method as follows:

> "For example, the B7 antigen is reacted with T cells *in vitro* to crosslink or aggregate the CD28 receptor, for example using CHO cells expressing B7 antigen, or immobilizing B7 on a solid substrate, to produce activated T cells for administration in vivo **for use in adoptive therapy. In adoptive therapy T lymphocytes are taken from a patient and activated *in vitro* with an agent.** The activated cells are then reinfused into the autologous donor to kill tumor cells (see Rosenberg et al., Science 223:1318-1321 (1986)). The method can also be used to produce cytotoxic T cells useful in adoptive therapy as described in copending U.S. Patent application serial no. 471,934, filed January 25, 1990, incorporated by reference herein" (emphasis added) (specification at page 24, first paragraph).

The *in vitro* data show that B7 is able to stimulate signal transduction and augment T cell activity by binding to CD28 (specification at page 68, lines 20-23). Further, Tables 2-4 show that binding of B7 to CD28 on T cells was costimulatory for T cell proliferation. This data plus the fact that B7/CD28 interactions normally occur in humans is applicants' basis for stating that the claimed methods involving the use of the claimed fusion proteins is taught in the specification.

There is no reason to believe that the B7 and CD28 or fusion proteins thereof would not be operable in humans *in vivo*. B7 and CD28 antigens are expressed in humans, i.e., human B cells (specification at page 6, lines 10-12). Such antigens normally exist and operate in humans. Applicants have discovered that one can use B7 to bind CD28 or CTLA4 and thus regulate certain T cells responses. The Examiner has not provided any reasons why the claimed fusion proteins would not work in humans since they are derived from portions of human antigens.

It is important to note that the claims are not limited to an *in vivo* use. The courts have held that in these instances the mere fact that the claimed invention may have possible utility

in vivo does not warrant disregard of *in vitro* activity where the claims are not limited to an *in vivo* use (*In re Isaacs and Lindenmann*).

Claims 1, 3, 5-10, 13-15, 17-24, 26-32, 47, 49, 51-66 and 77 are directed to methods of using B7, CD28, and fusion proteins thereof. For the reasons stated hereinabove, there is no basis for the rejection that applicants did not teach how to use the claimed methods in humans.

Applicants respectfully contend that with regard to the use of antibodies, the utility relied on is not directed to the treatment of humans. Therefore, clinical data is unnecessary (MPEP §608.01(p) at page 600-41).

The Examiner is requiring data from a recognized animal model using the claimed antibodies for *in vivo* use because Waldmann teaches that effective therapy using monoclonal antibodies has been elusive. Waldman describes limitations of murine antibodies in the therapy of human diseases due to the pharmacokinetic properties of rodent antibodies in human and human anti-mouse antibody responses.

The claimed invention is directed to monoclonal antibodies which recognize and bind CD28 or B7 and the uses of such antibodies. The *in vitro* data clearly show that the claimed antibodies recognize and bind their target (specification at Example I). There is no question as to this fact.

Waldman does not dispute the *in vitro* use of antibodies. In fact, Waldman merely teaches that effective therapy using unmodified monoclonal antibodies has been elusive for certain diseases such as cancer (Waldman at page 1657).

However, except for claim 59 which has been canceled without prejudice herein, the claimed invention is not directed to

therapy per se. Instead, the claimed invention is directed to methods of using the monoclonal antibodies to recognize and bind its target. Applicants provide data to substantiate this fact. In so binding to its target, the immune response is affected. Again applicants provide data to substantiate this fact.

In vivo data of the efficacy of these monoclonal antibodies is not required since the claims are not limited to merely *in vivo* use (*In re Isaacs,* supra). Moreover, like the applicants in *In re Isaacs*, applicants are not required to limit the claims to an *in vitro* use.

It is clear that the claimed invention can be administered using conventional modes of administration including, but not limited to, intravenous, intraperitoneal, oral, intralymphatic or administration directly into the tumor. Moreover, it would be clear to those skilled in the art that the most effective mode of administration and dosage regimen for the compositions of this invention depends upon the severity and course of the disease, the patient's health and response to treatment and the judgment of the treating physician. Accordingly, the dosages of the compositions should be titrated to the individual patient.

Further, applicants point out that applicants brought the Lenschow reference to the Examiner's attention to show that *in vitro* data herein correlates with *in vivo* results (specification at page 21, lines 1-9 and page 24, lines 6-12). In terms of the methods of using CD28 and fusion proteins thereof, there is no basis for the rejection that applicants did not teach how to use the claimed methods <u>in vivo</u>.

D. Lenschow et al. ((1992) Science <u>257</u>:789-792 entitled "Long Term Survival of Xenogeneic Pancreatic Islet Grafts Induced by CTLA4Ig" already of record) provided *in vivo* data in mouse

showing CTLA4Ig blocked the CD28 receptor from binding the B7 antigen results in manipulating the mouse immune system into accepting transplanted tissue instead of attacking it and thereby preventing the rejection of transplanted tissue.

Although different from CTLA4, CD28 shares with it some structural features, such as the precise number and relative position of cysteines, and a proline-rich stretch near the hydrophobic portion (Brunet et al., Immunol. Rev. 103:21-36, 30 (1988), annexed herewith as Exhibit 1). However, this does not mean that they render each other obvious in terms of their specific amino acid squences. This simply means that CTLA4 has predictive value for determining the behavior of soluble CD28 in vivo, i.e., CD28 or CD28Ig can bind the B7 antigen and at a higher concentration than CTLA4, soluble CD28 can block CTLA4 from binding the B7 antigen.

In light of the discussion hereinabove, applicants respectfully request that the Patent Office reconsider and withdraw the objection to the specification under 35 U.S.C. § 112, first paragraph.

REJECTION UNDER 35 U.S.C. §112

PARAGRAPH 21 OF THE OFFICE ACTION

In paragraph 21 of the Office Action, the Patent Office also rejected claims 1, 3, 5-15, 17-42, 47, 49, 51-57, 59-65, and 77 under 35 U.S.C. § 112 first paragraph, for the reasons set forth in the objection to the specification.

For the reasons discussed in connection with paragraph 20, applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §112.

PARAGRAPH 22 OF THE OFFICE ACTION

In paragraph 22 of the Office Action, the Patent Office rejected claims 1, 3, 5-10, 13-15, 17-42, 47, 49, 51-57, 59-65, and 77 under 35 U.S.C. §112, first paragraph, as the disclosure is allegedly enabling only for claims limited to *in vitro* regulation of T cell responses. The Examiner cited MPEP §703(n) and §703(z), i.e., claims corresponding to the specification and undue breadth, respectively.

Applicants respectfully traverse the Examiner's basis for rejection for the reasons discussed in paragraph 20.

PARAGRAPH 23 OF THE OFFICE ACTION

In paragraph 23 of the Office Action, the Patent Office rejected claims 9, 10, 56 and 57 under 35 U.S.C. § 112, first paragraph as the disclosure is allegedly enabling only for claims limited to immobilized B7 antigen on CHO cells.

In response applicants have amended claim 9 to recite "immobilized to eucaryotic host cells" as suggested by the Examiner.

PARAGRAPH 24 OF THE OFFICE ACTION

In paragraph 24 of the Office Action, the Office Action, the Patent Office rejected claims 13 and 14 under 35 U.S.C. § 112, first paragraph as the disclosure is allegedly enabling only for claims limited to *in vitro* use without the addition of a lymphokine.

Without conceding the correctness of the Examiner's statements and in order to further the prosecution of the subject application, applicants have canceled claims 13 and 14 without prejudice.

PARAGRAPH 25 OF THE OFFICE ACTION

In paragraph 25 of the Office Action, the Patent Office rejected claim 15 under 35 U.S.C. § 112, first paragraph, as the disclosure is allegedly enabling only for claims limited to use of the method in conjunction with anti-CD2. Allegedly, applicants' disclosure does not enable the use of the method with anti-CD3.

Applicants respectfully disagree with the Examiner's statements. However, in order to further the prosecution of the subject application, applicants have amended claim 15 to include anti-CD2.

PARAGRAPH 26 OF THE OFFICE ACTION

In paragraph 26 of the Office Action, the Patent Office also rejected claims 35-40 under 35 U.S.C. § 112, first paragraph, as the disclosure is allegedly enabling only for claims limited to the use of monoclonal antibody 9.3.

Applicants respectfully disagree with the Examiner's statements.

Applicants have enabled the use of all anti-CD28 monoclonal antibodies which recognize and bind a determinant site to which the monoclonal antibody 9.3 is directed. The monoclonal antibody 9.3 is deposited with the ATCC. One skilled in the art would have been able to identify anti-CD28 monoclonal antibodies which recognize and bind a determinant site to which the monoclonal antibody 9.3 is directed using conventional antibody competition assays (E. Harlow and D. Lane, eds., "Antibodies a laboratory manual" 1988, pages 567-577 annexed herewith as Exhibit 2). Other antibodies which recognize CD28 were well known. Further, applicants teach competition assays which would have permitted one skilled in

the art to identify antibodies which recognize and bind CD28 without undue experimentation.

Applicants respectfully contend that since the claimed invention is directed to methods for using certain anti-CD28 monoclonal antibodies, applicants are required under 35 U.S.C. §112, first paragraph to teach how to make and use the claimed method (specification at Example II, pages 44-54). However, applicants are not required to teach how to make all anti-CD28 monoclonal antibodies. It is sufficient in a method claim which uses antibodies that applicants teach how to use such antibodies since anti-CD28 monoclonal antibodies having the characteristics described in the claims are known and available. Applicants are required only to teach how to identify and use them which applicants respectfully contend they have. In so doing, applicants have fulfilled the requirements of 35 U.S.C. §112, first paragraph.

PARAGRAPH 27 OF THE OFFICE ACTION

In paragraph 27 of the Office Action, the Patent Office further rejected claims 1, 3, 5-10, 13-15, 17-24, 26-32, 35-42, 47, 49, 51-57, 59-65 and 77 under 35 U.S.C. § 112, first paragraph, as the disclosure is allegedly enabling only for claims limited to inhibiting the interaction of CD28 positive cells with B7 positive cells *in vitro*.

Applicants respectfully traverse the Examiner's statements for the reasons set forth in paragraphs 20 and 21 hereinabove.

PARAGRAPH 28 OF THE OFFICE ACTION

In paragraph 28 of the Office Action, the Patent Office rejected claim 17 under 35 U.S.C. § 112, first paragraph, as the disclosure is allegedly enabling only for claims limited to reacting CHO cells expressing B7 or fusion proteins with T-

cells.

Applicants respectfully disagree with the Examiner's statements. However, in order to further the prosecution of the subject application, applicants have amended claim 17 in accordance with the Examiner's suggestion, namely, to recite "The method of claim 1, wherein said T cells are reacted with B7 antigen or B7Ig and said T cell responses are stimulated".

PARAGRAPH 29 OF THE OFFICE ACTION

In paragraph 29 of the Office Action, the Patent Office also rejected claims 19-22 and 59-62 under 35 U.S.C. § 112, first paragraph, as the disclosure is allegedly enabling only for claims limited to using a B7 antigen reactive ligand which is either:

A) monoclonal antibody BB-1 or a $F(ab)_2$ fragment of said antibody, or

B) the CD28Ig fusion protein.

Applicants respectfully traverse the Examiner's basis for rejection.

Applicants have met the test of enablement. Applicants respectfully contend that since the claimed invention is directed to methods for using antibodies which recognize and bind B7 or fusion proteins which recognize and bind B7 so as to affect functional T cell responses, applicants are required under 35 U.S.C. §112, first paragraph to teach how to make and use the claimed method (specification at Examples II-III). Applicants' data support the claimed invention (specification at Examples I-III of the subject application).

One skilled in the art could have identified antibodies which recognize and bind a determinant site to which the monoclonal antibody BB-1 is directed using conventional antibody

competition assays (E. Harlow and D. Lane, eds., "Antibodies a laboratory manual" 1988, pages 567-577 annexed herewith as Exhibit 2). No undue experimentation would have been required.

In accordance with *United States v. Telectronics,* Inc., applicants are not required to teach how to make all anti-B7 monoclonal antibodies. Applicants are required only to teach how to identify and use them which applicants respectfully contend they have. In so doing, applicants have fulfilled the requirements of 35 U.S.C. §112, first paragraph.

For example, in a method comprising the use of a hammer as part of a mechanism to modulate temperature regulation, applicants would not be required to detail every possible hammer and how each is made. Instead, applicants would be required to describe and teach how use the hammer in the claimed method and disclose whether it is available, so that one skilled in the art could obtain a hammer meeting the specifications disclosed with what is already known in the art in order to make and use the claimed method.

PARAGRAPH 30 OF THE OFFICE ACTION

In paragraph 30 of the Office Action, the Patent Office also rejected claim 25 under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to monoclonal antibody BB-1. Allegedly, the specification does not enable every possible antibody to the B7 antigen.

Applicants respectfully disagree with the Examiner's statements. However, in order to further the prosecution of the subject application, applicants have canceled claim 25 without prejudice.

PARAGRAPH 31 OF THE OFFICE ACTION

In paragraph 31 of the Office Action, the Patent Office rejected claims 26-32 under 35 U.S.C. § 112, first paragraph, as the disclosure is allegedly enabling only for claims limited to the CD28Ig fusion protein containing amino acid residues from about position 1 to 134 and a second amino acid sequence corresponding to the hinge CH2 and CH3 regions of human Ig C-gamma-1.

In response, applicants have amended the claims in accordance with the Examiner's suggestion.

REJECTION BASED ON THE PRIOR ART

A. REJECTION BASED ON THE FREEMAN AND CAPON REFERENCES

In paragraph 32 of the Office Action, the Patent Office rejected claims 11 and 12 under 35 U.S.C. § 103 as being unpatentable over Freeman et al. (CA) in view of Capon et al. (CE) for reasons of record.

Applicants respectfully disagree with the Patent Office's position for the reasons which follow.

1. THE REJECTION IS BASED ON FACTUALLY FALSE ASSUMPTIONS

The essence of the rejection is that it would have been obvious to combine the extracellular portion of B7 with human Ig because Capon teaches CD4 Ig. Allegedly, Capon provides the motivation for the combination since Capon teaches that a fusion protein, i.e., the CD4Ig fusion protein, has a longer half life than the native, insoluble CD4 molecule.

This reasoning falsely assumes (1) that there is some similarity between B7 and CD4 which would suggest their

interchangeability and (2) that increasing the half life of any molecule whether it is of value or not is desirable or is meritorious and thus provides motivation to make the combination. Applicants respectfully reject both these arguments.

SEQUENCE SIMILARITY BETWEEN CD4 AND B7 ARE LESS THAN FIVE AMINO ACIDS

First, there is no similarity in function, structure, or any other property between CD4 and B7 (The Leucocyte Antigen Facts Book (1993) Barclay et al. (eds.) at pages 110-111 and pages 276-277 annexed herewith as Exhibits 3 and 4, respectively). In fact, there are no homologous regions of greater than five amino acids which are shared by CD4 and B7. The Examiner is respectfully reminded that the sizes of epitopes for protein or peptide antigens are typically about 9 to 15 amino acids (I. Wilson et al., "The Structure of an Antigenic Determinant", Cell 37:767-778 (1984) annexed herewith as Exhibit 5). Therefore, the short (less than five) amino acid similarity is insignificant.

B7 AND CD4 ARE NOT SIMILAR PROTEINS

Because B7 and CD4 are not similar proteins, the findings about the structure of CD4 have little, if any, predictive value for determining the behavior of B7. By the Examiner's reasoning, any molecule of the Ig superfamily could substitute for any other member, even those with a different number of domains; a different arrangement of domains; or disulfide bonds. This is contrary to what is known about the specificity and function of these molecules which depend on their three dimensional structure (Linsley et al., J. Exp. Med. 173:721-730 (1991) annexed herewith as Exhibit 7).

THERE IS NO EQUIVALENT SHOWING THAT THE FUNCTIONAL DOMAINS CAN BE INTERCHANGED THROUGHOUT THE IMMUNOGLOBULIN SUPERFAMILY

As applicants have argued previously, there is no equivalent showing that the functional domains can be interchanged throughout the immunoglobulin superfamily, whose members vary widely in structure. In fact, applicants data show that functional domains cannot be interchanged within the immunoglobulin superfamily without a loss in affinity and specificity (Linsley et al., J. Exp. Med. 173:721-730 (1991)).

BEFORE APPLICANTS' INVENTION, NO ONE HAD IDENTIFIED THE LIGAND WHICH BINDS B7

In fact, Freeman teaches only that "B7 expression was confined to several histologically defined subgroups of B cell malignancies" (Freeman at page 2714, abstract). However, this finding is not significant, i.e., B7 is not a marker for B cell malignancy, since it is not specifically expressed on neoplastic B lymphocytes but are also expressed on activated B lymphocytes (Freeman at page 2714, second column, second full paragraph).

The Patent Office's statements appear to be clearly a hindsight speculation of why someone would combine the cited references, which speculation is totally unrelated to the results of actually making the combination.

Not every molecule has a correlative ligand to which it binds. Since the function of B7 was unknown, there was no reason to suspect that B7 had such a correlative ligand let alone exert economic and intellectual resources to identify it.

2. THE REJECTION IS BASED ON INAPPLICABLE LEGAL STANDARDS

The rejection of the Patent Office appears to be contrary to the guidance provided by the Federal Circuit as to how references can be combined.

In *In re Sernaker* (702 F.2d 989, 217 USPQ 1 (Fed. Cir. 1983)), the Federal Circuit postulated two related tests for determining obviousness based on the prior art as follows.

> "(a) whether a combination of the teachings of all or any of the references would have suggested (expressly or by implication) the possibility of achieving further improvement by combining such teachings along the line of the invention in suit, and,
>
> (b) whether the claimed invention achieved more than a combination which any or all of the prior art references suggested, expressly or by reasonable implication."

THERE IS NO SUGGESTION TO COMBINE THE REFERENCES

There is no motivation to substitute a claimed compound (B7) for the prior art compound (CD4) unless the two compounds share a common utility (*In re Lalu and Foulletier* 747 F.2D 703, 223 USPQ 1257 (Fed. Cir. 1984).

CD4 AND B7 DO NOT SHARE A COMMON UTILITY

CD4 and B7 do not share a common utility. CD4 recognizes and binds gp120 and thus is involved in modulating HIV (Freeman at page 2714).

Further, it is clear that the mere combination of prior art references does not make an invention obvious unless something in the prior art suggests or reasonably implies an advantage to be derived from uniting their teachings. Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 806 F.2D 1565, 1 USPQ2d 1081 (Fed. Cir. 1986). Increasing the serum-half life of a molecule for which no use is known is not an advantage. It provides nothing more than a molecule for which no use is known and which is able to circulate longer in serum.

Before applicants' invention, no one had identified the ligand which binds B7 or B7's function. Applicants were the first to discover that B7 recognizes and binds CD28 and CTLA4 antigens.

Because it binds such antigens, B7 is involved in modulating CTLA4/B7 and/or CD28/B7 antigen-mediated T cell responses.

The Examiner stated that the processes as taught by Capon for making **any** fusion protein is routine (Paper No. 16 at page 11, first paragraph). Further, the combination of references provides motivation to make and used the claimed invention (Id).

The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification. *In re Laskowski,* 871 F.2d 115, 117, 10 USPQ2d 1397, 1398 (Fed. Cir. 1989). The question is not simply whether the prior art teaches the particular element of the invention, but whether it would suggest the desirability, and thus the obviousness, of making the combination. *Carella v. Starlight Archery,* 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986).

HAVING MORE OF SOMETHING WHICH HAS NO KNOWN USE OR INCREASING THE HALF-LIFE OF SOMETHING WHICH HAS NO KNOWN USE DOES NOT PROVIDE MOTIVATION TO MAKE IT

The Examiner stated that the motivation for the combination would have been the making of a soluble B7 protein with a long serum half life (Paper No. 12). Before applicants' invention no one knew the function of B7. No one knew if it even had a ligand let alone that it would bind CTLA4 and CD28. A protein having no known function or ligand but having a longer serum half-life is of no real value. One is still left with the dilemma of what to do with it. Why spend the time and economic resources to produce a fusion protein having a longer half-life than its naturally occurring counterpart if no use is known?

Without suggestion or motivation to produce the B7Ig, one is merely picking and choosing among the individual elements of

assorted prior art references to recreate the claimed invention. It is well established in patent law that this practice is impermissible to establish obviousness. *Smithkline Diagnostics, Inc. v. Helena Laboratories Corp.*, 859 F.2d 878, 887, 8 USPQ2d 1468, 1475 (Fed. Cir. 1988).

There must be a reason or suggestion in the art for selecting which extracellular domain to use other than the knowledge learned from applicants' disclosure. *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1988). However, the cited references provide none.

For these reasons, applicants respectfully contend that the cited references did not provide or suggest a motivation to produce the claimed invention. Therefore, the cited references fail alone or in combination to render obvious the claimed invention.

In view of the aforementioned discussion, applicants respectfully request that the Patent Office reconsider and withdraw the rejection of claims 2-3 under 35 U.S.C. §103.

REJECTION BASED ON THE YOKOCHI REFERENCE

The Patent Office rejected claim 25 under 35 U.S.C. § 103 as allegedly unpatentable over Yokochi et al. (CD). Claim 25 is drawn to a monoclonal antibody reactive with the B7 fusion protein. The Patent Office stated that Yokochi et al. produced monoclonal antibody BB-1.

In response, applicants have canceled claim 25.

REJECTION BASED ON THE ARUFFO AND CAPON REFERENCES

The Patent Office rejected claims 33 and 34 under 35 U.S.C. § 103 as being unpatentable over Aruffo et al. (AV) in view of

Capon et al. (CE) for reasons of record.

Applicants respectfully disagree with the Patent Office's position.

THE COMBINATION OF ARUFFO AND CAPON DOES NOT RENDER OBVIOUS THE CLAIMED INVENTION

The analysis for the obviousness of the CD28 Ig is similar to that stated by applicants with regard to the B7 Ig as set forth in response to paragraph 32 of the Office Action. Specifically, the law requires that there be some similarity between CD28 and CD4 which would suggest their interchangability. Like, B7, there is no similarity in function, structure, or any other property between CD4 and CD28 (The Leucocyte Antigen Facts Book (1993) Barclay et al. (eds.) at pages 110-111 annexed herewith as Exhibit 2 and at pages 162-163 annexed herewith as Exhibit 6, respectively). In fact, there are no homologous regions of greater than five amino acids which are shared by CD4 and CD28. Since the sizes of epitopes for protein or peptide antigens are typically about 9 to 15 amino acids, the short (less than five) amino acid similarity is insignificant.

In view of the lack of similarity between CD4 and CD28, the structure of CD4 have little, if any, predictive value for determining the behavior of CD28.

Further, a combination of reference teachings is improper unless the prior art suggests such a combination. *In re Sernaker,* 702 F.2d 989, 217 USPQ 1 (Fed. Cir. 1983).

There is no suggestion to combine the references because there is no motivation to substitute a claimed compound (CD28) for the prior art compound (CD4) unless the two compounds share a common utility (*In re Lalu and Foulletier* 747 F.2D 703, 223 USPQ 1257 (Fed. Cir. 1984).

CD4 and CD28 do not share a common utility. CD4 recognizes and binds gp120 and thus is involved in modulating HIV. In contrast, CD28 recognizes and binds the B7 antigen and thus is involved in modulating CTLA4/B7 and/or CD28/B7 antigen-mediated T cell responses.

Moreover, increasing the serum-half life of a molecule for which no use is known is not an advantage. It provides nothing more than a molecule for which no use is known and which is able to circulate longer in serum.

Before applicants' invention, no one had identified the function of CD28. Applicants were the first to discover that CD28 is involved in modulating CTLA4/B7 and/or CD28/B7 antigen-mediated T cell responses.

The Examiner is incorrect in stating that since the processes as taught by Capon for making **any** fusion protein is routine, the combination of references provides motivation to make and used the claimed invention (Paper No. 16 at page 11, first paragraph).

The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification. In re Laskowski, 871 F.2d 115, 117, 10 USPQ2d 1397, 1398 (Fed. Cir. 1989). The question is not simply whether the prior art teaches the particular element of the invention, but whether it would suggest the desirability, and thus the obviousness, of making the combination. *Carella v. Starlight Archery,* 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986).

The Examiner stated that the motivation for the combination would have been the making of a soluble B7 protein with a long serum half life (Paper No. 12). However, before applicants' invention no one knew the function of CD28.

The fact that a fusion protein of unknown function and without a known ligand could be made and could be made to have a longer half-life than its naturally occurring counterpart does not provide the motivation to produce the fusion protein. Producing such a molecule would have been analogous to making something which you do not need and for which no use was known. Why do it?

Applicants respectfully contend that without suggestion or motivation to produce the CD28Ig, one is merely picking and choosing among the individual elements of assorted prior art references to recreate the claimed invention. It is well established in patent law that this practice is impermissible to establish obviousness. *Smithkline Diagnostics, Inc. v. Helena Laboratories Corp.*, 859 F.2d 878, 887, 8 USPQ2d 1468, 1475 (Fed. Cir. 1988).

For these reasons, applicants respectfully contend that increasing the half life of a molecule is not motivation to make it unless one skilled in the art has a practical use for it other than merely as a reagent to find its use, i.e., using it merely research purposes. Therefore, the cited references fail alone or in combination to render obvious the claimed invention.

PARAGRAPH 36 OF THE OFFICE ACTION

The Examiner rejected claim 21 under 35 U.S.C. §112, second paragraph, as allegedly indefinite.

In accordance with the Examiner's suggestion, applicants have amended claim 21 to include --CD28-- and deleting "CD 28".

CONCLUSION

In view of the aforementioned discussion, applicants

respectfully request that the Patent Office reconsider and withdraw the rejection under 35 U.S.C. §103.

Because of the preceding discussion and amendments, applicants request that the Patent Office reconsider and withdraw the various grounds for objection and rejection set forth in the Office Action and earnestly solicit allowance of the claims now being examined.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone her at the number provided below.

No fee, other than the $360.00 extension fee, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 19-2090.

Respectfully submitted,

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I hereby certify that this paper is being deposited this date with the U.S. Postal Service as first class mail addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Signature 12/13/93 Date